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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	20

DATE MAILED: 09/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/520,489	TSCHOPP, JURG	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *39-42,46,48 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *39-42,46,48 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 36 and 43-45 have been canceled. Claims 39-42, 46, and 48 have been amended. Claims 39-42, 46, 48 and 49 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

The rejection of claims 36 and 39-45 under 35 U.S.C. 102(e) as being anticipated by Wiley (U.S. 6,171,787) are withdrawn in light of applicants arguments.

New Grounds of Rejection

Claim 48 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear if the recitation "fragment thereof" in claim 48 refers to the polypeptide encoded by SEQ ID NO:1 or to the antibody which binds to said polypeptide.

Claims 39-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The first paragraph of 35 U.S.C. 112 states that "the specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of

experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ (CCPA 1977)). Additionally the courts have determined that "...where a statement is , on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factor are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The instant claims are drawn to a method of treating, suppressing or altering the progression of a cancer comprising the administration of an effective amount of an antibody directed to an APRIL ligand polypeptide capable of interfering with an interaction between said APRIL ligand polypeptide and an APRIL receptor, in combination with a chemotherapeutic agent. The APRIL receptor was not identified at the time of filing. The specification does not teach the identity of the APRIL receptor. Without knowing the identity of the receptor, one of skill in the art would be subject to undue experimentation in order to carry out method claims directed to antagonizing or interfering with the binding of APRIL to its receptor.

Claims 39-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claim are drawn to methods dependent upon the identity of the APRIL ligand. The specification teaches on page 7, line 24 to page 8, line 2, that the APRIL of the instant invention encompasses sequences having at least 50% homology with DNA sequences encoding the C-terminal receptor binding portion of APRIL, wherein said sequence encode SEQ ID NO:1 or a protein having similar biological activity. Thus the instant

method claims are dependent on the identitiy of a genu of proteins, wherein said proteins can have "similar" biological activity and 50% sequence identity to the human or murine proteins disclosed by the specification. The human or murine sequences fail to anticipate the genus of APRIL proteins contemplated by the specification because the genus tolerates numerous structural alterations within a 50% sequence identity and functional attributes which could identify members of the genus are not specifically disclosed, ("similar" biological activity does not limit the proteins to the identical biological activity of the disclosed human and murine sequences and the metes and bounds of what constitutes a "similar" activity in contrast to non-similarity cannot be determined from the specification. One of skill in the art would conclude that applicant failed to disclose a representative number of species that would serve to describe the claimed genus. ..

Claims 46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hori et al (Biochemical and Biophysical Research Communications, 1991, Vol. 174, pp. 758-766) and Kamijo et al (Biochemical and Biophysical Research Communications, 1989, Vol. 158, pp. 155-162) and Tsujimotot et al (Lymphokine Research, 1989, Vol 8, pp. 99-106), all as evidenced by Wiley (U.S. 6,171,787 and in view of Yu et al (WO 96/14328).

Claim 46 is drawn to a method for identifying an agent capable of suppressing the growth of a cell culture comprising the steps of identifying a cell that proliferates in response to the binding of a polypeptide encoded by SEQ ID NO:1 to its cell surface receptor; growing said cell in said cell culture; exposing said cell culture to a compound resulting in an exposed cell culture; concurrently or subsequently exposing said exposed cell culture to the polypeptide encoded by SEQ ID NO:1, or a fragment thereof; comparing the proliferation of said cell within said exposed cell culture to the proliferation of a substantially identical cell in a second cell culture that was not exposed to said compound; and determining whether said compounds has suppressed the growth of said cell in said exposed cell culture. Claim 48 embodies the method of claim 46 wherein said compound is an antibody directed to the polypeptide encoded by SEQ ID NO:1 or a fragment thereof.

Wiley teaches that the instant SEQ ID NO:2 as human TNF gamma (SEQ ID NO:2) (column 6, lines 41-42) as well as soluble human TNF-gamma (SEQ ID NO:3), (column 57, lines 27-28). Thus, TNF-gamma is the polypeptide encoded by SEQ ID NO:1.

Hori et al teach a method for identifying an agent capable of suppressing the growth of a fibroblast cell culture comprising the steps of identifying fibroblasts as cells that proliferate in response to TNF-gamma, growing said cells in culture, exposing said cells to prostaglandin, wherein said prostagladins antagonize the mitogenic effect of TNF-gamma (abstract and figure 1).

Tsujimotot et al teach that TNF gamma and beta inhibited the TNF-mediated growth stimulation of human fibroblasts (abstract and figure 2).

Kamijo et al teach a method for identifying an agent capable of suppressing the growth of a fibroblast cell culture comprising the steps of identifying fibroblasts as cells that proliferate in response to TNF-gamma, growing said cells in culture, exposing said cells to transforming growth factor-beta, wherein said TGF-beta antagonizes the mitogenic effect of TNF-gamma (abstract and figure 1). Kamijo et al note that the inhibition of the mitogenic effect of TNF was not attributable to down regulation of the TNF receptor, nor to alteration of the affinity of TNF for its receptor (page 160, lines 2-4). Kamijo et al further teach that the suppressive activity of TGF-beta was abolished when L-929 cells were treated with actinomycin D or cycloheximide, suggesting that TGF-beta might inhibit the action of TNF via a de novo protein synthesis. Kamijo et al teach that although the suppression of this TNF induced cytotoxicity by TGF-beta is only partial;, the suppression of fibroblast proliferation by TGF-beta is complete, suggesting the existence two intracellular pathways for TGF cytotoxicity induction, wherein one of these pathways is not identical to that needed for cell proliferation.

All of Hori et al, Kamijo et al and Tsujimotot et al teach that human fibroblast are mutagenically stimulated by the presence of TNF-gamma in culture. Neither Hori et al, Kamijo et al nor Tsujimotot et al teach the interference of this stimulation by blocking the interaction between TNF-gamma and the TNF-gamma receptor.

Yu et al specifically teach that antibodies specific for TNF-gamma may be used as antagonists by binding to TNF-gamma and preventing it from binding to its receptor (page 22, second paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute an antibody which specifically binds to TNF-gamma for the compounds of prostaglandin, TNF-gamma and TNF-beta and TGF-beta in the method rendered obvious by the combination of Hori et al and Kamijo et al and Tsujimotot et al and Wiley and Yu et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Yu et al on antibodies which bind to TNF-gamma as antagonists of the binding of TNF-gamma to its receptor, and the teachings of Kamijo et al on the presence of alterative intracellular pathways induced by TNF which are not needed for the intracellular pathway which induces cell proliferation. One of skill in the art would be motivated to antagonize the biding of TNF-gamma from its receptor to discern if the activation of the TNF receptor were responsible for the cell proliferation signal induced by TNF.

Claims 46, 48 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hori et al (Biochemical and Biophysical Research Communications, 1991, Vol. 174, pp. 758-766) and Kamijo et al (Biochemical and Biophysical Research Communications, 1989, Vol. 158, pp. 155-162) and Tsujimotot et al (Lymphokine Research, 1989, Vol8, pp. 99-106), and Wiley (U.S. 6,171,787 and Yu et al (WO 96/14328) as applied to claims 46 and 48 above, and further in view of Aggarwal et al (FEBS, 1995, Vol. 372, pp. 44-48).

Claim 49 is drawn to the method of claim 46, wherein said cell is a tumor cell.

The combination of Hori et al and Kamijo et al and Tsujimotot et al and Wiley and Yu et al render obvious the claimed method wherein the cell is a normal fibroblast; neither of Hori et al and Kamijo et al and Tsujimotot et al and Wiley nor Yu et al teach the cell as a tumor cell.

Aggarwal et al teach that several glioma cell lines are resistant to the antiproliferative effect of tumor necrosis factor (page 47, second column, lines 14-15). Aggarwal et al teaches that many factors have been implicated in the modulation of tumor cell growth by TNF including tumor oncogenes (page 44, first column, lines 1-7 and second column, lines 8-13)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute tumor cells in the method for identifying an agent

capable of suppressing the growth of a cell culture comprising the steps of identifying a cell that proliferates in response to the binding of a polypeptide encoded by SEQ ID NO:1 to its cell surface receptor; growing said cell in said cell culture; exposing said cell culture to a compound resulting in an exposed cell culture; concurrently or subsequently exposing said exposed cell culture to the polypeptide encoded by SEQ ID NO:1, or a fragment thereof; comparing the proliferation of said cell within said exposed cell culture to the proliferation of a substantially identical cell in a second cell culture that was not exposed to said compound; and determining whether said compounds has suppressed the growth of said cell in said exposed cell culture. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Aggarwal et al on the correlation between oncogene expression and resistance to TNF. One of skill in the art would be motivated to understand the molecular basis for tumor necrosis factor resistance as it directly relates the success or failure of anti-tumor protocols encompassing TNF as an anti-tumor agent.

All other rejections and objections as set forth in Paper No. 14 are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
9/8/03